UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY and MANULIFE INSURANCE COMPANY, Plaintiffs, v. ABBOTT LABORATORIES, Defendant.	CIVIL ACTION NO. 05-11150-DPW

ABBOTT'S CORRECTED DEPOSITION COUNTER-DESIGNATIONS FOR JEANNE M. FOX

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached corrected deposition counter-designation for the May 17, 2007 deposition of Jeanne M. Fox, Divisional Vice President of the North American Regulatory Affairs.

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Dated: February 22, 2008

Respectfully submitted,

ABBOTT LABORATORIES

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CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 22, 2008.

Date: February 22, 2008

/s/ Ozge Guzelsu

Jeanne Fox Deposition Designations

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
05/17/07	Fox, Jeanne	5:5-5:19					
05/17/07	Fox, Jeanne	25:19-27:7			2	HZ	
05/17/07	Fox, Jeanne	40:10-41:3					
05/17/07	Fox, Jeanne	45:17-46:4					
05/17/07	Fox, Jeanne	46:24-47:10			3	ID	
05/17/07	Fox, Jeanne	48:1-48:8			3	ID	
05/17/07	Fox, Jeanne	49:10-49:18			3	ID	
05/17/07	Fox, Jeanne	51:3-51:6			3	ID	
05/17/07	Fox, Jeanne	55:19-57:15			4	IG	
05/17/07	Fox, Jeanne	57:22-58:8			4	IG	
05/17/07	Fox, Jeanne	60:15-60:17			5	IE	
05/17/07	Fox, Jeanne	61:11-62:22			4	IG	
05/17/07	Fox, Jeanne	74:18-75:3					
05/17/07	Fox, Jeanne	77:2-77:18					
05/17/07	Fox, Jeanne	78:9-78:22			4	IG	
05/17/07	Fox, Jeanne	82:12-82:20			4	IG	
05/17/07	Fox, Jeanne	95:15-96:2			6	IF	
05/17/07	Fox, Jeanne	114:23-115:24			8	IO	
05/17/07	Fox, Jeanne	116:24-117:14					
05/17/07	Fox, Jeanne	129:6-129:16			10	IQ	
05/17/07	Fox, Jeanne	131:3-131:17			10	IQ	
05/17/07	Fox, Jeanne	133:22-134:20			10	IQ	

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
05/17/07	Fox, Jeanne	136:11-137:17			10	IQ	
05/17/07	Fox, Jeanne	138:1-138:6			10	IQ	

Color Key to Deposition Designations

Designation by Plaintiffs

Counter Designation by Defendants

Designation by Defendants

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE)
COMPANY, JOHN HANCOCK VARIABLE)
LIFE INSURANCE COMPANY and)
MANULIFE INSURANCE COMPANY)
(f/k/a INVESTORS PARTNER)
INSURANCE COMPANY),)
Plaintiffs,) Civil Action No.
-vs-) 05-11150-DPW
ABBOTT LABORATORIES,)
Defendant.)

CONFIDENTIAL

THE VIDEOTAPED DEPOSITION OF

JEANNE FOX

May 17, 2007

in the witness, please.

(WHEREUPON, the witness was duly sworn.)

MR. ZWICKER: Ready?

JEANNE FOX,

called as a witness herein, having been first duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. ZWICKER:

Q. Good morning, Ms. Fox.

A. Good morning.

Q. Is it Ms. or Dr. or something else?

A. Ms. is fine.

Q. Ms. is fine. Where do you work?

A. I work at Abbott Laboratories.

Q. What's your job there?

A. I'm the senior director in global pharmaceutical regulatory affairs, heading up the U.S. regulatory affairs area.

Q. How long have you had that position?

A. I've been direct -- senior director of U.S. regulatory affairs since January of 2004.

Q. What are your responsibilities as global pharmaceutical regulatory affairs director?

A. I'm responsible for managing the U.S. regulatory affairs group that works to get products approved in the U.S. and keep the products on the market and the applications current and compliant.

We have responsibility for promotional review and approval as well as making routine submissions.

Q. Are you responsible from a regulatory standpoint for all drugs under development by Abbott in the United States?

A. No.

Q. What portion of Abbott's drugs under development are you responsible for in your present position?

A. Presently my group is responsible for the development of U.S.-only opportunities.

Q. So that means if Abbott is going to market a drug in the U.S. and outside of the U.S., you wouldn't be involved, is that right?

A. If they are going to develop a drug globally, I would not be involved.

Q. How many drugs --

MR. PHILLIPS: Can I --

MR. ZWICKER: Sure.

that point in time. So, there might have been someone else who made a specific filing if I needed the assistance.

BY MR. ZWICKER:

Q. Who was on your staff?

A. Matt Biondi I believe was with me during that time frame. Alexa Chun was with me during that time frame. Rebecca Welch worked for me. Greg Bosco.

Q. What did Greg Bosco do with respect to 773?

A. With respect to 773, he made a number of the submissions to the IND.

Q. What else?

A. He would have prepared the regulatory submissions. He would have been responsible for seeing that the -- the actual clinical drug release was done correctly within regulatory.

(WHEREUPON, a certain document was marked Fox Deposition Exhibit No. 2, for identification, as of 05-17-2007.)

MR. ZWICKER: Before the witness is Fox Exhibit No. 2, which is an e-mail and covering

document dated September 13, 2000, and it bears Bates Nos. ABBT 557552 through 557.

BY MR. ZWICKER:

Q. Ms. Fox, could you review Exhibit 2 and let me know when you are done.

A. I'm finished.

Q. Do you recognize this document?

A. I don't remember it.

Q. Do you recognize the form of it?

A. Yes.

Q. What is it?

A. For a period of time we were asked to prepare a section of a larger development plan for compounds and the section was specific to regulatory strategy and it had a prescribed format to it.

Q. What role did you play in the preparation of those documents?

A. They were prepared within the regulatory group. So, either myself or someone working for me would have drafted these in discussion with the team.

Q. And you would have either written them or reviewed them?

A. Correct.

Q. What would you review them for? What was your purpose in reviewing them?

A. Regulatory accuracy.

Q. So, you wanted make sure that the content of these documents was accurate. Fair?

A. From a regulatory perspective.

Q. What does that mean?

A. For instance, in Section D.3, the table indicates what guidance documents were used to assess what the requirements would be.

Q. Not your hunt?

A. Pardon?

Q. That's not your -- that's not what you were looking to -- that's not what you were focusing on, D.3, right?

Let me ask you a different question.

A. I don't understand the question.

Q. Look at D.1, "Regulatory Strategy SWOT Analysis."

A. All right.

Q. You would have taken responsibility for ensuring the accuracy of this portion of the document, right?

testing to document that -- that a particular class or a particular compound had absolutely no effect.

So, part of the challenge for us would be to get FDA agreement on what it would take in terms of how we would conduct the studies, whether we would put EKG monitoring in the studies, how we would do the assessment to satisfy their request to see documentation that the product did not have the potential to prolong QT.

Q. Abbott had the concern in -- as of September 2000 that the FDA was scrutinizing QT issues closely. Is that fair?

MR. PHILLIPS: Objection; lack of foundation as to what Abbott thought or was concerned about.

BY THE WITNESS:

A. My recollection is that in the -- in the regulatory arena at that time, FDA was very much looking at QT prolongation as a -- as a new issue that they would have to define how to study, how to label.

BY MR. ZWICKER:

Q. And was your recollection that the FDA hadn't provided very much guidance to drug manufacturers about how it would consider the issue

and what it would require to get comfort that a drug was safe?

A. That is my recollection.

Q. What is your understanding of what a class issue is in connection with QTc prolongation and as referred to in this document?

MR. PHILLIPS: Objection; vague, lack of foundation.

BY THE WITNESS:

A. From a regulatory standpoint, when something is considered a class issue, that generally means FDA looks across a particular group of compounds that are related either by structure or by activity, and they look for that group of compounds to behave similarly.

BY MR. ZWICKER:

Q. Was your recollection that the FDA -- well, strike that.

In your experience if the FDA looks across a class of compounds to determine whether they behave similarly, in your experience could that have implications for delaying FDA approval in bringing drugs to market?

MR. PHILLIPS: Objection; incomplete

Q. And NDA is New Drug Application?

A. That's correct.

MR. ZWICKER: Would you like a break?

THE WITNESS: No, I think I'm all right.

MR. ZWICKER: We have been going for a little over an hour.

MR. PHILLIPS: Are you sure? Maybe we should take a brief break, just stretch our legs.

THE VIDEOGRAPHER: We are going off the video record at 10:11 a.m. This concludes Tape No. 1.

(WHEREUPON, a recess was had from 10:11 to 10:22 a.m.)

THE VIDEOGRAPHER: We are going back on the video record at 10:22 a.m. This is the beginning of Tape No. 2.

BY MR. ZWICKER:

Q. Ms. Fox, do you recall attending or participating in a teleconference with the FDA in November of 2000 where the FDA put a halt on Abbott's Phase III clinical trials for 773?

MR. PHILLIPS: Objection; assumes facts not in the record.

BY THE WITNESS:

A. I recall that we had a teleconference

with FDA around the beginning of the Phase III clinical trials. To my recollection, the FDA at that point in time asked us to suspend enrollment in the clinical trials.

BY MR. ZWICKER:

Q. Why did the FDA ask you to suspend enrollment in the clinical trials?

MR. PHILLIPS: Well, objection; calls for speculation.

You may answer if you understand the question.

BY THE WITNESS:

A. I don't remember the details of the discussion.

BY MR. ZWICKER:

Q. What was the purpose of that teleconference, do you recall?

A. I don't remember if we asked for the teleconference or they asked for it.

Q. You participated in it?

A. Yes.

MR. ZWICKER: Let's mark this as the next exhibit.

(WHEREUPON, a certain document was

marked Fox Deposition Exhibit
No. 3, for identification, as of
05-17-2007.)

MR. ZWICKER: Before the witness is Exhibit No. 3, which is an e-mail from Jeanne Fox to various persons and a covering FDA contact report.

BY MR. ZWICKER:

Q. Ms. Fox, could you review this document and let me know when you're done.

MR. PHILLIPS: Counsel, just one question for the record.

Do you know if the circle on the first page is in the original document? I don't recall.

MR. ZWICKER: You know, Greg, I've come to appreciate that level of meticulousness from you. And, in fact, that -- that is my circle.

MR. PHILLIPS: Oh, okay. Thank you.

I will take it as a compliment. I'm not sure it was intended as such.

MR. ZWICKER: It was intended as one.

BY MR. ZWICKER:

Q. Ready?

A. Yes.

Q. Ms. Fox, did you -- just looking at the FDA contact report, which is -- ends in Bates No. 682, did you write this FDA contact report?

A. It appears that I did.

Q. And do you believe that it was accurate and complete when you wrote it?

A. My practice is to make them accurate and complete.

Q. Did you submit it to anyone for review who participated in the call?

A. I don't recall if I would have done that or not.

Q. What was the purpose of your preparation of this FDA contact report?

A. To communicate to my manager and to the rest of the team what the outcome of the teleconference was.

Q. I notice from the first page, which is an e-mail from you to various persons, that you sent it to John Leonard. Do you see that?

A. Yes, I see his name.

Q. Why did you send it to John Leonard?

A. I believe that it was sent to John Leonard because the project team that we worked

with at that point in time would have reported in to John Leonard.

Q. Does reviewing this document help you recall that the subject of the November 20 contact with the FDA related to toxicology issues?

A. That's what it states under "Subject of Call."

Q. You remember that?

A. Yes.

Q. Do you remember that the FDA was dissatisfied with Abbott's efforts regarding toxicology studies and QTc and liver toxicity?

MR. PHILLIPS: Objection; vague.

BY THE WITNESS:

A. I recall that they were asking us to do additional toxicology work and that they were asking that based on information that they told us they were not at liberty to share with us.

BY MR. ZWICKER:

Q. They were asking you to do additional toxicology work based on information that they couldn't share with you, is that what you're saying?

A. Yes.

Q. And did you -- you participated in this call, correct?

A. Yes.

Q. Were you the lead Abbott representative on the call, do you recall?

A. I would have been the senior regulatory representative on the call.

Q. Would you have done most of the talking?

A. Not necessarily.

Q. It's fair to say that the FDA wasn't satisfied with the toxicology results to date submitted by Abbott relating to QT and liver toxicity. Is that fair?

A. I don't believe I would characterize it that way. They were asking us to do an additional study.

Q. And the study they wanted you to do would emphasize liver toxicity and QTc, correct?

A. It would evaluate the drug's use in dogs to assess the potential for QT prolongation and to assess -- to evaluate for hepatotoxicity.

Q. Going into the call, did you believe that the toxicity work that Abbott had done to date was satisfactory?

A. Yes, I believe that was my understanding going into this telephone call.

Q. Is it fair to say that you were surprised by the FDA's insistence on additional toxicology work?

A. Yes.

Q. And did the FDA's request for additional work cause you to believe that the FDA was taking liver toxicity and QT issues very seriously?

A. I think it meant that they were -- they were concerned enough about these two issues in general that they wanted to make sure that we specifically evaluated them in the way they were recommending for this product.

Q. Were you surprised by their level of concern?

A. I don't think that it is extremely unusual that this kind of issue might arise during development.

Q. Did you have any discussions with anyone on the 773 team after the November 20th FDA contact?

MR. PHILLIPS: I'm sorry. Objection; vague. You mean about the contact?

follow that feedback, you are likely to -- to be able to file an NDA without FDA changing their position.

BY MR. ZWICKER:

Q. And an NDA is -- essentially marks approval of the drug for commercialization?

A. It's the application that you submit to get marketing approval.

Q. Did you in fact participate in the End of Phase II meeting with the FDA?

A. Yes, I believe I did.

Q. Was that an in-person meeting or was it a teleconference?

A. That was an in-person meeting.

Q. Do you recall who else participated with you or attended with you?

A. I believe Carl Craft was in attendance. I don't recall who else was there.

(WHEREUPON, a certain document was marked Fox Deposition Exhibit No. 4, for identification, as of 05-17-2007.)

MR. ZWICKER: Before the witness is Fox Exhibit No. 4, which is an e-mail and a series of

covering slides.

BY MR. ZWICKER:

Q. Ms. Fox, if you wouldn't mind reviewing this document and letting me know when you're done.

All done?

A. Yes.

Q. Just looking at the e-mail, it's an e-mail authored by you, correct?

A. It appears to be.

Q. And is this your attempt to summarize the significant events at the End of Phase II meeting?

A. I can't tell that from this document. It just looks like it's slides for an upcoming meeting.

(WHEREUPON, a certain document was marked Fox Deposition Exhibit No. 5, for identification, as of 05-17-2007.)

MR. ZWICKER: Before the witness is Fox Exhibit No. 5, which is an FDA contact report bearing Bates Nos. 205257 through 259.

BY MR. ZWICKER:

Q. Ms. Fox, if you could look at that

contact report and let me know if it refreshes your recollection regarding whether the slides that are attached to this e-mail summarize the contact with the FDA on November 27, 2000.

MR. PHILLIPS: Object to the form.

BY THE WITNESS:

A. Could you repeat the question?

BY MR. ZWICKER:

Q. Yes, of course.

Does reviewing Exhibit No. 5, which is the FDA contact report, help you recall that the Exhibit 4 and the accompanying slides are your attempt to summarize the FDA contact on November 27?

A. They appear to be.

Q. Let's just look at your e-mail for a minute. You start by saying. "OK, here's my first draft of slides for the Leiden meeting."

You prepared these slides by yourself or with someone else's assistance?

A. I don't remember.

Q. And you believe that the slides you prepared accurately reflect what took place at the FDA contact on November 27, correct?

MR. PHILLIPS: Object to the form.

BY THE WITNESS:

A. My practice is to accurately reflect what happened at FDAs -- any interaction with the FDA.

Q. And you have no reason to think you deviated from that practice in this instance?

A. No, I do not.

Q. You write, "I guess after our meeting on Monday, the only major issues identified which are still open are QT, liver and resistant pathogens, so that's what I focus on with some general comments at the end."

Do you see that?

A. I see that statement.

Q. Did you mean that the only major issues open with the FDA are QT, liver and resistant pathogens? Is that what you meant?

A. I don't recall what I meant.

Q. You characterized those issues as major issues. Do you see that?

A. I see that that's what it says, yes.

Q. And that's because you believe the issues were important from the FDA's perspective,

meeting with the FDA an important meeting in connection with obtaining regulatory approval from the FDA?

MR. PHILLIPS: Objection; vague.

BY THE WITNESS:

A. I think, as I said earlier, it's one of the prescribed meetings that you're allowed to have and it's a good way to get feedback so that when you get ready to submit at the end of Phase III you've done work that they recognize will satisfy their requirements and will -- will hopefully allow you to have the label that you're planning to have at approval.

BY MR. ZWICKER:

Q. Take a look at Exhibit 5, which is the FDA contact report. You wrote that, correct?

A. I believe so.

Q. Look at the Abbott representatives on page 1.

A. Yes.

Q. And is this list consistent with your practice that everyone on it attended the meeting for Abbott?

A. Yes.

Q. You recall John Leonard being there?

A. No, I don't.

Q. Do you recall Carol Meyer being there?

A. No, I don't.

Q. What do you remember the discussion at the November 27, 2000 contact involving regarding QTc prolongation?

A. I don't remember the specifics of the discussion. All I see is what's written here on the page.

Q. Take a look at your slides and specifically page 1, which is Bates numbered 818, the last three digits anyway.

A. Okay.

MR. PHILLIPS: That's Exhibit 4, counsel, is that right?

MR. ZWICKER: Yes.

BY MR. ZWICKER:

Q. The first bullet says, "ABT-773 Potential for QTc Prolongation."

Do you see that?

A. "QT Prolongation," yes.

Q. Yeah. It says, the next line does, "QT issue is hot button for FDA."

Do you see that?

A. Yes.

Q. Are those your words or the FDA's?

A. Probably mine.

Q. Why did you choose them?

A. Because that's a slang way to represent an issue that seems to be a topical issue for FDA. So, in other words, it's prominent at the time. It's important. You have to be aware of it. You have to address it. Issues come and go with FDA. They get resolved. If they're moving into a new area.

As I said earlier, QT was one of those issues that, when it started to become of interest to FDA, then they had to assess how it should be studied, what kind of direction they were going to be giving to sponsors and ultimately what kind of assessment would lead to what kind of label.

Q. You said that issues come and go with the FDA. Would you agree that in November of 2000 QT prolongation was a hot button issue for the FDA?

A. It was a prominent issue right then.

Q. The next line down, you say, "Question whether ketolides behave like macrolides."

A. I don't recall the discussion around that issue.

BY MR. ZWICKER:

Q. The last bullet point says, "Plan to conduct routine liver monitoring in all Phase III studies."

Do you see that?

A. Yes.

Q. Do you recall whether or not Abbott's decision to conduct routine liver monitoring in Phase III studies came as a result of the FDA's concern about liver toxicity?

A. No, I don't recall.

MR. PHILLIPS: I'm sorry. I wanted to interpose an objection that the question assumes facts not in the record.

BY MR. ZWICKER:

Q. What do you recall the discussion about Abbott's intention to seek a resistance claim at the November 27th meeting at the FDA?

A. I recall that they had not completely defined what the burden of proof would be in terms of the number of isolates. There was no written guidance at that point in time. There was some

discussion around whether we could pool isolates across different infectious diseases to reach a higher total number.

Q. Did you feel that in some respects that Abbott was in the dark with respect to what would be required to achieve a resistance claim?

MR. PHILLIPS: Objection; vague.

BY THE WITNESS:

A. I don't think I would characterize that as being Abbott being in the dark as much as FDA not having made up its mind -- made up its mind what would be considered adequate proof.

BY MR. ZWICKER:

Q. And if the FDA hadn't made up its mind regarding what would be considered adequate proof, then Abbott, you, would be uncertain whether or not you could achieve a resistance claim, correct?

MR. PHILLIPS: Objection; vague as to what you mean by "you."

BY THE WITNESS:

A. I think the purpose of the discussion at the meeting was to try to propose something that would get us -- get Abbott a claim for resistance for ABT-773 and try to get FDA to concur what that

discussion.

Q. How about just for you. Were you uncertain whether Abbott could achieve a resistance claim after the November 27 meeting?

MR. PHILLIPS: Objection; vague.

BY THE WITNESS:

A. I think gaining the claim depended on finding the isolates. I think we had a reasonable discussion with FDA so that we had an idea of what it would take.

But the -- the actual ability to achieve that was completely dependent on our ability to find patients with resistant organisms and to successfully treat them.

BY MR. ZWICKER:

Q. And you didn't know whether you'd be able to do that, right?

A. Correct.

MR. PHILLIPS: Objection; vague as to what you mean by "you."

BY MR. ZWICKER:

Q. Take a look at Exhibit No. 4, the page ending 821, the last three digits.

You write in the first bullet

point, "Indication to treat resistant pathogens."

Do you see that?

A. Yes.

Q. Was that your way of saying that Abbott will be seeking an indication to seek resistant pathogens?

A. I think it was a way of introducing the topic of getting an indication.

Q. The next bullet point says, "FDA skepticism regarding clinical significance of 'macrolide-resistant S." pneumoniae or "pneumo," which I assume is short for pneumonia.

What did you mean by that?

A. I recall the discussion around this issue at the meeting was that FDA was uncertain of what the actual clinical significance of macrolide-resistant Strep pneumo was.

So, what that meant was it would be up to us to provide enough data and documentation that would actually provide proof that if someone had a macrolide-resistant Strep pneumo that was a pathogen that would -- that would cause harm.

MR. PHILLIPS: I'm sorry. Could you read back that response, please.

Q. Are you saying that the FDA was uncertain whether there was such a thing as a macrolide-resistant strep pneumonia?

A. No. I'm saying they were uncertain how that would translate into clinical disease.

Q. So, you're saying that the FDA was concerned in fact whether a macrolide-resistant strep pneumonia was in fact a -- a serious illness?

MR. PHILLIPS: Objection; lack of foundation, vague.

BY THE WITNESS:

A. I think the agency was looking for us to provide proof that macrolide-resistant Strep pneumo existed in a form that had clinical relevance and clinical ramifications.

BY MR. ZWICKER:

Q. What do you mean by "clinical relevance and clinical ramifications"?

A. Well, in a patient with -- with an illness as opposed to in a test tube.

Q. Is it fair to say that the FDA was concerned whether macrolide-resistant Strep pneumo was a serious health problem? Is that fair?

MR. PHILLIPS: Objection; calls for

that was discussed.

Q. Penicillin was the other?

A. Yes.

Q. You write in your slide that the FDA was -- expressed skepticism regarding clinical significance of macrolide-resistant S. pneumoniae.

Did you understand the FDA to be skeptical regarding Abbott's ability to prove that the problem existed, could be treated and that you would be able to have efficacy with it?

Let me ask you a different question.

What do you mean when you say "skepticism" in this line?

A. I believe that I would have used the term to -- to ill' -- to describe that FDA had told us that they weren't -- they didn't have data in their hands at that point in time that said that macrolide-resistant Strep pneumo is a clinical concern. So, we would have to develop that data for them.

Q. And speaking for yourself, were you uncertain whether that could be done?

A. That wasn't my call to judge that.

Q. Did you have discussions with others

Q. Okay.

MR. ZWICKER: Do you want to change the tape?

THE VIDEOGRAPHER: We are going off the video record at 11:39 a.m. This concludes Tape No. 2.

(WHEREUPON, a recess was had from 11:39 to 11:51 a.m.)

THE VIDEOGRAPHER: We are going back on the video record at 11:51 a.m. This is the beginning of Tape No. 3.

(WHEREUPON, a certain document was marked Fox Deposition Exhibit No. 6, for identification, as of 05-17-2007.)

BY MR. ZWICKER:

Q. Ms. Fox, before you is Exhibit No. 6, which is an e-mail from you to various persons dated November 28, 2000.

Could you review it and let me know when you're done.

A. Okay.

Q. Any reason to doubt that you wrote this e-mail?

A. No.

Q. And having reviewed it, any doubts in

your mind about its accuracy?

A. No.

Q. You sent it to -- you cc'd Carol Meyer on it. Do you see that? At the bottom. She's right before Greg Bosco.

A. Yes.

Q. Why?

A. She worked on the project team at that time. I don't remember the role that she had.

Q. Did you have a lot of contact with her?

A. Not that I remember.

Q. The very last sentence in the e-mail, you say, "In addition, we were directed to modify" all our -- "all of our informed consents to inform patients that QT prolongation has been seen with related classes of drugs and therefore may be a risk with ABT-773."

Did you do that? Did Abbott do that? Did it modify its consents?

MR. PHILLIPS: Objection; lack of foundation.

BY THE WITNESS:

A. I don't remember, but I presume we did.

BY MR. ZWICKER:

Q. Whose job would it have been to do that?

development and FDA review because if they develop issues, then FDA may very well come back to the follow-on products and ask you to do additional work, ask you to look at the product in a way that may be new or different or under more scrutiny.

(WHEREUPON, a certain document was marked Fox Deposition Exhibit No. 8, for identification, as of 05-17-2007.)

MR. ZWICKER: Before the witness is Exhibit No. 8, which is an ABT-773 Update February 12, 2001.

BY MR. ZWICKER:

Q. Ms. Fox, could you review this document and let me know when you're done.

A. Okay.

Q. Just focusing on the headings marked "QTc Issues," "Liver Toxicity Issues." Did you write these sections of this document?

A. No, I don't believe so.

Q. Do you know who did?

A. No.

Q. The document is titled "ABT-773 Update February 12, 2001."

MR. PHILLIPS: Objection; vague.

BY THE WITNESS:

A. From the -- from the reading of the sentence, yes.

BY MR. ZWICKER:

Q. Look at the section marked "Liver Toxicity Issues," which is going back to --

A. Which document?

Q. Yeah, my apologies. Going back to Exhibit 8 and it's beginning on page 043 and carrying over to 044.

A. Tell me again where you're looking.

Q. Beginning on 043.

A. Which section?

Q. "Liver Toxicity Issues."

A. Okay.

Q. Now, turn the page -- I will read you the paragraph.

"The FDA has similar concerns regarding the potential for liver toxicity of new drugs as it has for QT issues, since both of these problems have resulted in drugs being removed from the market shortly after approval. The concerns have been directed at the quinolones, but all

antimicrobials are undergoing extensive evaluations. The FDA has a meeting on guidance to industry on how to study the potential for liver toxicity scheduled for February 11 and 12, 2001. Jeanne Fox will attend this meeting and report back on it so we will be able to update this topic at the February meeting."

Do you see that?

A. Yes.

Q. Did you attend a meeting in February of 2001 regarding the FDA's views on liver toxicity?

A. Yes.

Q. Where was the meeting?

A. It was in Washington D.C.

Q. Who sponsored it?

A. I think it was co-sponsored between FDA and another group, but I can't recall what the other group would have been.

MR. PHILLIPS: Excuse me. Since the witness' microphone fell off, I just want to make sure. Were all of her responses recorded?

THE VIDEOGRAPHER: Yes, I can --

MR. PHILLIPS: Thank you.

THE WITNESS: Doesn't want to stay on that

lapel for some reason.

BY MR. ZWICKER:

Q. Did you attend that meeting with anyone or did you go alone?

A. I don't recall if there were any other Abbott attendees.

Q. Were there handouts?

A. I think there was probably an agenda. At some later point I believe the slides were made available probably on an FDA web site.

Q. Did you keep a copy?

A. I don't remember if I --

Q. How long was the conference?

A. Two or three days.

Q. You stayed for all of it?

A. Yes, I believe so.

Q. Who presented?

A. I don't remember specific names. There were a number of different presenters, both academia, FDA. There might have been some industry presenters as well.

Q. And the entire conference was devoted to liver toxicity and antibiotics?

A. No.

Q. What was the conference devoted to?

A. It was -- I would more characterize it as almost a seminar on what do we know about hepatotoxicity caused by drugs and how do we develop data and screening tests so that when we bring drugs into clinical development, we may have a better ability to predict which ones might cause issues.

Part of what FDA was encouraging was that there be more sharing of data from, in particular, the products that had been pulled from the market for liver toxicity.

FDA was encouraging those sponsors to consider sharing that data so that they -- they could retrospectively look at the clinical trials that were conducted and perhaps find a way to say, "Oh, yeah, that was a signal. We just didn't see it at that point in time."

Q. Were there any portions of the conference devoted to liver toxicity and antibiotics?

A. I believe it was discussed.

Q. Do you -- what do you recall about the discussion between liver toxicity and antibiotics?

A. I don't recall any specifics.

Q. Do you recall generally that the FDA expressed a concern at the conference about the relationship between liver toxicity and antibiotics?

A. I think this conference was not too long after one of the major quinolones was removed from the market, Trovan, and that was a product where the company had developed a clinical safety database of 10 to 11,000 patients prior to approval.

So that the discussion was around the size of that database and the, you know, the inability to see even with that number of patients a signal that would have predicted hepatotoxicity.

Q. What's a safety database?

A. It's the -- the term for the safety assessment of all of the patients that you have in your clinical trials. FDA calls that your safety database.

Q. For all phases, 1, 2 and 3?

A. Yes.

Q. Did you come away from the meeting you attended in Washington in 2001 with the

understanding that the FDA was carefully scrutinizing liver toxicity issues in antibiotics under development?

A. I came away with the impression that FDA was going to be scrutinizing any signs and signals and evaluations for liver toxicity for all development compounds and probably for marketed products as well.

Q. How did that impact your thinking about what you would have to do to convince the FDA that 773 was safe for the liver?

A. I don't know that I came away from that meeting with any sound or any specific conclusions that there was a -- a path forward that was prescribed. So, in other words, study this many patients, do this, do that, and we'll consider you safe.

It was more of an academic meeting where the take-home was we don't have all the answers but we're going to be looking very carefully, which then, you know, convinced me that it was an issue for all Abbott products under development, that we would have to be very aware of and very thorough with our assessment.

Q. Were you more or less optimistic that you could achieve regulatory approval for 773 after the meeting?

MR. PHILLIPS: Objection; assumes facts not in the record.

BY THE WITNESS:

A. I don't believe I looked at that meeting and its results as anything that would have impacted my assessment of any of the programs that we had underway.

BY MR. ZWICKER:

Q. Turn to -- on page 044, there is a section that begins with "773 IV Formulation Program."

Do you see that?

A. Yes.

Q. Turn the page. It says, "The IV formulation program is presently unfunded."

Do you see that?

A. Yes.

Q. Did you know that, that as of February 2001 that the IV program was unfunded?

A. I don't recall.

Q. Given your attendance at FDA meetings in

2000, did you believe that it was important for Abbott to fund an IV program in connection with achieving a resistance claim for 773?

MR. PHILLIPS: Objection; vague.

BY THE WITNESS:

A. I -- I think my impression was that having the IV product would have made running the IV to oral stepdown studies much more practical and doable.

BY MR. ZWICKER:

Q. And in terms of achieving a resistance claim, an IV program would have been a positive factor?

A. I believe so.

Q. Look at the same paragraph I read you, the very last bullet, it says, "Provide additional information on QTc effects."

Do you see that?

A. Yes.

Q. Can you explain how an IV program would have provided information on QTc effects?

MR. PHILLIPS: Objection; lack of foundation.

BY THE WITNESS:

A. No, I can't.

True?

A. Correct.

MR. PHILLIPS: I'm going to object that the question is argumentative. You used the word "though."

(WHEREUPON, a certain document was marked Fox Deposition Exhibit No. 10, for identification, as of 05-17-2007.)

MR. ZWICKER: The record should reflect that before the witness is Fox Exhibit No. 10, which is a series of e-mails bearing Bates No. 568172.

BY MR. ZWICKER:

Q. Ms. Fox, could you review Exhibit 10 and let me know when you're done.

A. Okay.

Q. Do you recognize this document?

A. I don't recall the document specifically, no.

Q. Do you recall the issue that the document relates to?

MR. PHILLIPS: Objection; vague.

BY THE WITNESS:

A. Yes, pediatric rule requirements were a

Do you see that?

A. Yes, I see the statement.

Q. Do you remember an issue in February of 2001 at Abbott regarding failure to fund pediatric programs for compounds under development?

A. Not specifically, I don't recall that.

Q. What about generally?

A. Generally I remember that the first several years after the pediatric rule requirement came into effect that -- excuse me.

Q. Sure.

A. The project teams were not used to planning pediatric programs early in the process. They were used to waiting until they -- they had a lot of data in hand on the adult program to make decisions about whether to take a given product into pediatrics.

And, so, it was a -- it was a time where we as the regulatory contributors to the project teams had to keep reminding them that you now have a new requirement to meet. You now have to plan your pediatric programs. You have to start your development of your pediatric dosage forms sooner because at some point you will reach the point

where you're ready to submit an application for the adult and FDA will have expectations that you tell them how you intend to meet the pediatric rule.

So, it was a -- a period of a couple of years where it was getting the teams familiar with the requirements and making sure that they started thinking ahead.

Q. When did the pediatric rule come into effect?

A. I don't remember the actual effective date.

Q. Was the 2001 period part of the period where persons on development teams were not paying sufficient attention to the pediatric rule?

MR. PHILLIPS: Well, objection to the extent it mischaracterizes the testimony, assumes facts not in the record.

BY THE WITNESS:

A. I wouldn't say that they weren't paying attention. They weren't familiar with the rule or the requirements. They were being encouraged by their regulatory representative to start planning sooner in the process. I believe that period of time was around 2000, 2001.

BY MR. ZWICKER:

Q. During this period of time?

A. I believe so.

Q. And is it fair to say if you went to the FDA seeking an NDA and didn't have your -- and hadn't satisfied the pediatric rule, the FDA might deny your application?

MR. PHILLIPS: Objection; lack of foundation, calls for speculation.

BY THE WITNESS:

A. I believe that was a theoretical possibility that had not been put to the test.

BY MR. ZWICKER:

Q. In your experience did it ever happen that the FDA denied an NDA for failure to satisfy the pediatric rule?

A. I don't know.

Q. That you can remember in your experience.

A. In my experience in the products that I worked on, not to my recollection.

Q. You write back, returning to the e-mail now, "I share your concern and have an even bigger one. In those cases where we are planning to

develop an NCE and we have" an NDA -- "a target NDA date, I have had difficulty convincing people that they have to take the pediatric rule requirements seriously."

What's an NCE?

A. New chemical entity.

Q. Is 773 an NCE?

A. Yes.

Q. Did you have a target NDA date for 773 as of --

A. I believe we did.

Q. You say, "I have difficulty convincing people to take the pediatric rule requirements seriously."

Did you encounter that problem with respect to 773 in 2001?

MR. PHILLIPS: Objection; vague.

BY THE WITNESS:

A. Based on this e-mail, I believe it probably was the case.

BY MR. ZWICKER:

Q. What people did you have in mind when you wrote this sentence?

A. Probably the project team.

MR. PHILLIPS: Well, let me just caution Ms. Fox that don't speculate. Your use of the term "probably" in the last two answers suggests possibly that you are speculating.

THE WITNESS: Okay.

BY MR. ZWICKER:

Q. The project team was composed of whom?

A. The venture team at that point in time I believe was under the direction of Dr. Carl Craft perhaps.

Q. What about Stanley Bukofzer? Was he involved at that time?

A. I don't remember when he became involved.

Q. Do you recall having difficulty convincing Carl Craft to take the pediatric rule requirement seriously?

A. I don't recall that.

Q. Do you recall any conversations with anyone, even if you can't identify them specifically, regarding a difficulty in convincing that person to take the pediatric rule requirement seriously?

A. No, I don't remember.

Q. But you have no doubt since you wrote this e-mail that you must have had such difficulties with some persons, right?

MR. PHILLIPS: Objection; calls for speculation.

BY THE WITNESS:

A. Since I wrote the e-mail, that was -- that was apparently what my thinking was at the time.

BY MR. ZWICKER:

Q. The next sentence you have is, "The answer I keep getting on ABT-773 is 'but that project isn't funded.' I don't think the FDA will buy that answer."

Do you recall who gave you the answer that the pediatric studies for 773 aren't funded?

A. No.

Q. But you don't doubt that somebody gave you that explanation based on this e-mail, right?

A. Based on the e-mail.

Q. Is it fair to say that you were frustrated by the 773 development team's inattention to the pediatric rule?

MR. PHILLIPS: Objection; mischaracterizes the

testimony.

BY THE WITNESS:

A. I don't recall that I would say frustrated. All I -- all I have to go on is what I see before me.

BY MR. ZWICKER:

Q. Well, clearly you're not happy about it, right?

MR. PHILLIPS: Objection and calls for speculation.

BY THE WITNESS:

A. I think the e-mail was a response to one of my colleagues raising this as a -- as a global issue and I indicated that I shared the concern.

BY MR. ZWICKER:

Q. For 773?

A. Specifically for 773.

Q. And you conclude by saying, "I don't think the FDA will buy that answer."

Do you see that?

Is that your way of saying that the FDA won't approve an NDA unless the pediatric rule is satisfied?

A. No.

Q. What are you saying when you say "I don't think the FDA will buy that answer"?

A. If the answer is that the project isn't funded, that would not be an acceptable response to a question from FDA about the -- the pediatric studies.

Q. As of February 14, 2001, as far as you knew, based on this e-mail, the pediatric program wasn't funded, right?

MR. PHILLIPS: Objection; lack of foundation.

BY THE WITNESS:

A. I don't remember.

BY MR. ZWICKER:

Q. You write, "The answer I keep getting is 'but that project isn't funded.'"

Do you see that?

A. Yes, I see that.

Q. Does that cause you to conclude that as of February 14, 2001, the pediatric program wasn't funded?

MR. PHILLIPS: Objection; calls for speculation, lack of foundation.

BY THE WITNESS:

A. It tells me that when I wrote this

204097

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE)
COMPANY, et al.,)
Plaintiffs,) Civil Action No.
-vs-) 05-11150-DPW
ABBOTT LABORATORIES,)
Defendant.)

I hereby certify that I have read the foregoing transcript of my deposition given at the time and place aforesaid, consisting of Pages 1 to 183, inclusive, and I do again subscribe and make oath that the same is a true, correct and complete transcript of my deposition so given as aforesaid, and includes changes, if any, so made by me.

Jeanne M. Fox
JEANNE FOX

SUBSCRIBED AND SWORN TO
before me this 14th day
of June , A.D. 2007.

Notary Public
Dalea M Luna

OFFICIAL SEAL
DALEA M. LUNA
NOTARY PUBLIC, STATE OF ILLINOIS
My Commission Expires June 26, 2007

Errata Sheet

Page: 1 Of Total Pages: 10

I wish to make the following changes to my deposition/statement:

Page #: 7, Line #: 21

As appears in Transcript: Weden

To: Wheadon

Reason: misspelling

Page #: 8, Line #: 9

As appears in Transcript: two years

To: 14 months

Reason: incorrect subtraction

Page #: 11, Line #: 9

As appears in Transcript: Yeah

To: Yes

Reason: grammar

Page #: 13, Line #: 19

As appears in Transcript: to

To: at

Reason: grammar

6/14/07
DATE

Elaine M. Fox
DEPONENT'S SIGNATURE

Errata Sheet

Page: 2 Of Total Pages: 10

I wish to make the following changes to my deposition/statement:

Page #: 28, Line #: 16
As appears in Transcript: Could be me
To: It could be me
Reason: grammar

Page #: 29, Line #: 1
As appears in Transcript: Um-hmm.
To: Yes.
Reason: grammar

Page #: 30, Line #: 3
As appears in Transcript: don't have
To: can't provide
Reason: clarification

Page #: 31, Line #: 8
As appears in Transcript: was
To: were
Reason: grammar

6/14/07
DATE

Adanne M. Fox
DEPONENT'S SIGNATURE

Errata Sheet

Page: 3 Of Total Pages: 10

I wish to make the following changes to my deposition/statement:

Page #: 39, Line #: 18
As appears in Transcript: U
To: —
Reason: typo

Page #: 42, Line #: 19
As appears in Transcript: What's I believe more . . .
To: What I believe is more . . .
Reason: grammar

Page #: 43, Line #: 5
As appears in Transcript: I don't Know that answer.
To: I don't recall.
Reason: Clarification

Page #: 43, Line #: 14
As appears in Transcript: I don't Know how that was identified.
To: I don't remember.
Reason: Clarification

6/14/07
DATE

Jeanne M. Fox
DEPONENT'S SIGNATURE

Errata Sheet

Page: 4 Of Total Pages: 10

I wish to make the following changes to my deposition/statement:

Page #: 53, Line #: 5
As appears in Transcript: were
To: was
Reason: grammar

Page #: 54, Line #: 16
As appears in Transcript: That--that can be--that path...
To: That path...
Reason: redundant - clarify

Page #: 58, Line #: 4
As appears in Transcript: what happened at FDAs--any...
To: what happened during any...
Reason: clarification

Page #: 60, Line #: 12
As appears in Transcript: that you're planning to...
To: that you would like to...
Reason: clarification

6/14/07
DATE

Jeanne M. Foy
DEPONENT'S SIGNATURE

Errata Sheet

Page: 5 Of Total Pages: 10

I wish to make the following changes to my deposition/statement:

Page #: 68, Line #: 3
As appears in Transcript: how best to -- to assess
To: how best to assess all
Reason: clarification

Page #: 75, Line #:
As appears in Transcript: would get us -- get Abbott
To: would get Abbott
Reason: clarification

Page #: 78, Line #: 21
As appears in Transcript: Strep pneumo that was a
To: Strep pneumo, it was a
Reason: clarification/grammar

Page #: 87, Line #: 12
As appears in Transcript: get the patients
To: get the number of patients
Reason: clarification

6/14/07
DATE

Jeanne M. Fox
DEPONENT'S SIGNATURE

Errata Sheet

Page: 6 Of Total Pages: 10

I wish to make the following changes to my deposition/statement:

Page #: 89, Line #: 5
As appears in Transcript: supporting that that
To: Supporting that, which
Reason: grammar

Page #: 91, Line #: 10
As appears in Transcript: I don't know that -- I don't recall...
To: I don't recall...
Reason: redundant

Page #: 92, Line #: 4
As appears in Transcript: assessment of my trying to...
To: assessment of my attempt to...
Reason: clarification

Page #: 92, Line #: 13
As appears in Transcript: The -- this time...
To: This time...
Reason: redundant

6/14/07
DATE

Jeanne M. Fox
DEPONENT'S SIGNATURE

Errata Sheet

Page: 7 Of Total Pages: 10

I wish to make the following changes to my deposition/statement:

Page #: 92, Line #: 23
As appears in Transcript: use in children, whether -- unless...
To: use in children, or unless...,
Reason: clarification

Page #: 98, Line #: 1/2/3
As appears in Transcript: It's typically for any given project a portfolio review would be made to the senior...
To: Typically a portfolio review would be made for any given project to the senior...
Reason: clarification/grammar

Page #: 99, Line #: 5
As appears in Transcript: I would have assumed
To: I would assume
Reason: grammar

Page #: 107, Line #: 19
As appears in Transcript: as we -- we've had it earlier
To: as we said it earlier
Reason: clarification

6/14/07
DATE

Jeanne M. Fox
DEPONENT'S SIGNATURE

Errata Sheet

Page: 8 Of Total Pages: 10

I wish to make the following changes to my deposition/statement:

Page #: 107, Line #: 21
As appears in Transcript: in FDA's sites at . . .
To: in FDA's sights at . . .
Reason: misspelling

Page #: 113, Line #: 2
As appears in Transcript: It was -- I would more characterize
To: I would characterize
Reason: clarification/grammar

Page #: 108, Line #: 3
As appears in Transcript: So, I think that that . . .
To: So, I think that . . .
Reason: grammar

Page #: 112, Line #: 12
As appears in Transcript: I don't remember if I --
To: I don't remember.
Reason: clarification

6/14/07
DATE

Jeanne M. Fox
DEPONENT'S SIGNATURE

Errata Sheet

Page: 9 Of Total Pages: 10

I wish to make the following changes to my deposition/statement:

Page #: 117, Line #: 6
As appears in Transcript: I -- I think my impression was that
To: I think my understanding was that
Reason: clarification

Page #: 142, Line #: 1
As appears in Transcript: development, approval of ...
To: development and approval of ...
Reason: clarification

Page #: 160, Line #: 15
As appears in Transcript: was necessary to get -- an IV program was necessary
To: was necessary
Reason: redundant/repetitive

Page #: 165, Line #: 8
As appears in Transcript: I think what I said was FDA looking at
To: I think what I said was FDA was looking at
Reason: clarification

6/14/07
DATE

Jeanne M. Fox
DEPONENT'S SIGNATURE

Errata Sheet

Page: 10 Of Total Pages: 10

I wish to make the following changes to my deposition/statement:

Page #: 167, Line #: 4
As appears in Transcript: Centered for -- excuseme. Center For
To: Center For
Reason: Clarification

Page #: 171, Line #: 11
As appears in Transcript: Oh, I think I -- my group probably
To: Oh, I think my group probably
Reason: Clarification

Page #: 79, Line #: 21
As appears in Transcript: Strep pneumo that was
To: Strep pneumo, it was
Reason: to match correction on pg 78 line 21

Page #: _____, Line #: _____
As appears in Transcript: _____
To: _____
Reason: _____

6/14/07
DATE

Elaine M. Fox
DEPONENT'S SIGNATURE

Deposition Exhibit 2

P's Exhibit HZ

Gregory Bosco/LAKE/PPRD/ABBOTT
09/13/2000 12:44 PM

To Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT
cc George Ayntilian/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject ABT-773 Dev Plan

Carol,

Here's the PPD Regulatory piece. Jeanne has reviewed it.

Greg

Development Plan - 9-00.doc

CONFIDENTIAL
ABBT0557552

EXHIBIT
Fox 2
5-17-07

Gregory Bosco/LAKE/PPRD/ABBOTT

09/13/2000 12:44 PM

To Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT
cc George Ayrilian/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject ABT-773 Dev Plan

Carol,

Here's the PPD Regulatory piece. Jeanne has reviewed it.

Greg

Development Plan - 9-00.doc

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EXHIBIT
Fox 2
5-17-07

D. Regulatory Strategy

D.1 Regulatory Strategy SWOT Analysis

Table D.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)

CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	• QD dosing may be viewed as positive for patient compliance if data is strong	Make sure PK/PD data is available to support dose selection rationale
	• If the drug has a favorable risk benefit ratio with added value compared to existing therapies then the likelihood of approvability is high in EU countries or other countries requiring a CPMP package	The development programs must be designed to unequivocally demonstrate the existence of an added value (e.g. safety or clinical efficacy against resistance species)
	• ABT-773 may present a key point of differentiation with promising activity against macrolide and penicillin resistant *Streptococcus pneumoniae* and enhanced antibacterial activity *in vitro*. If proven *in vivo*, this may indicate favourable relative therapeutic value required for approval and inclusion within local use guidelines. For COFs countries, if the US or EU receives approval then approvals in these LA/PAA countries are assured assuming appropriate sourcing.	To utilize the enhanced bacterial activity as a key point of differentiation need to: • Ensure clinical program is designed to optimize chances of obtaining desired isolates • Ensure appropriate pk/pd studies are performed • Seek agreement from FDA regarding burden of proof for labeled indication against resistant pathogens
Weaknesses	• Take with food labeling is required to reduce AE's	FDA will still require pivotal bioavailability studies to be done in fasted state.
	• If BID is chosen for either CAP or ABS, diurnal variation may become an issue during FDA review	Justification must be provided
	• Conformance to Abbotts' & FDA's Electronic Document Management System requirements may impact filing date	Electronic filing likely to be valued very highly by FDA, so need to manage internal process to see that we can meet requirements
	• High COG's for bulk drug driving vendor matrix and push to redefine starting material	Need FDA buy-in from End-of-Phase 2 CMC meeting on starting material and vendor matrix, including stability requirements Communicate with team, international

	Harmonization of global clinical trial designs and guidelines • Differences in medical practice exist worldwide for antibiotics and associated infections • Differences in comparator and dosing regimens • Stringent EU regulatory environment with antibiotics	affiliates, international experts and discuss with EU authorities through agency meetings to ensure design of trials and comparators are acceptable
	EU filing will require a harmonized labeling therefore country-speicific favourable labeing cannot be pursued (as done with clarithromycin)	Discuss any country specific issues with authorities, international experts and affiliates. Monitor regulatory environment and competitive products.
	Two dose scenario with a lower dose chosen for ABECB, Sinusitis and Pharyngitis with a second dose chosen for CAP may provide limited numbers to assess safety of the higher dose	Discuss issue authorities at agency meeting and ensure MAA addresses this issue. May consider Phase IV studies to address this concern.
	Increased resistance awareness may influence stricter requirements and trend away from lowest effective dose	Ensure clinical program includes relative pk/pd studies and can demonstrate clear efficacy at proposed doses. Ensure clinical program is designed to obtain resistance isolates
Opportunities	• Labeling for resistant organisms if isolates are obtained	Get agreement with FDA at End of Phase 2 meeting regarding number of isolates required for labeling claim
	Eligible for Centralised filing process which would provide EU-wide 10 year protection . May also file by Mutual Recognition procedure which more provides flexibility for non-harmonized disease practices (e.g. infectious disease/antibiotics)	Filing strategy to be determined based on strength of the clinical program and advice received from agencies during planned agency meetings
	Once Daily Dosing may enhance compliance	
Threats	• QT prolongation class labeling in Warnings section of labeling	Get agreement with FDA at End of Phase 2 meeting regarding EKG monitoring in Phase 3 and promote theory that QT prolongation is not class related Ensure that non-clinical and clinical program fulfill the CPMP points to consider on QTc prolongation.
	• Liver enzyme increases in Warnings section of	Ensure that non-clinical and clinical

	labeling • Possible failure of short course therapy for Pharyngitis due to more stringent Test of Cure requirement from FDA • If gastrointestinal AE's are high, may affect benefit/risk assessment by FDA • Could be affected by CDC push to reduce antibiotic use: reserve use of drugs effective vs resistant organisms until existing therapies have failed	program addresses potential safety labeling issues and MAA/NDA addresses these concerns.

D.2 Registration Strategy and Timelines for Filing

Table D.2 Registration Strategy and Timelines for Submission

REGION	Proposed Submission Date	Justification
US	• August 2002	Estimated completion of the clinical program and CMC stability data
Europe Filing procedure (Centralised or MRP) to be determined based on strength of clinical data and discussion with authorities	August 2002	Estimated completion of the chemistry/pharmacy and clinical data
Japan Plan to bridge to US data assuming pk profile is similar in Japanese subjects and a successful Phase II bridging study is possible in Japan	TBD	Bridging obviates the need for a lengthy and expensive Japanese Phase III program. Requires Kiko agreement.

D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program

Table D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program

COUNTRY	Guideline Requirement	Probability of Achieving	Impact on Filing	Impact on Approvability
US	• Draft Anti-Infective Guidances for CAP, ABECB, ABS & Pharyngitis	High	High	High
	• Draft Anti-Infective Guidances – General Considerations for Clinical Trials	High	High	High
	• Anti-Infective Points to Consider document	High	High	High
	• ICH Efficacy Guidances – E1 through E12	High	High	High
	• ICH Safety Guidances - S1 through S7	High	High	High
	• ICH Quality Guidances – Q1 through Q7	High	High	High
Europe	All ICH guidelines as above, plus CPMP points to consider on QT prolongation CPMP guideline on the clinical evaluation of antibacterials DRAFT CPMP guideline for pk/pd	High/Moderate	High	High
Japan	All ICH guidelines as above plus local guidelines/JP issues. ICH E5 ethnic bridging guideline.	Moderate/Unknown	High	High

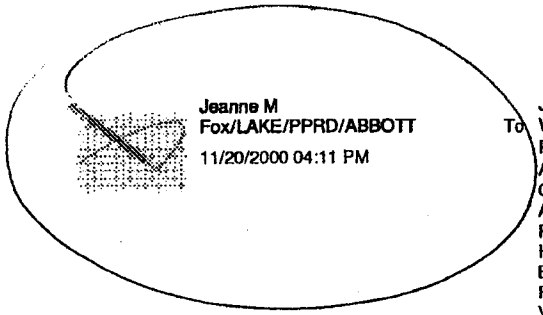
D.4 Table of Proposed Discussions with Health Authorities

Table D.4 Table of Proposed Discussions with Health Authorities

COUNTRY	Reason for Discussion	Proposed timing for Discussion
US	• End of Phase 2 -- Clinical	10/2000
	• End of Phase 2 -- CMC	TBD
	• Pre-NDA -- Clinical	TBD
	• Pre-NDA -- CMC	TBD
Europe	• Individual agency meetings with UK, Germany, France and Spain to discuss Phase III Clinical program trial designs	UK complete – 07/10/00 Germany complete- 07/21/00 France scheduled – 08/30/00 Spain -- to be determined
	• Pre-filing meetings to be determined based on filing strategy	
Japan	• KIKO- discuss bridging strategy to 300 mg EU/US program	Complete – June 2000
	• KIKO -- re-discuss dose justification	TBD

Deposition Exhibit 3

P's Exhibit ID



Jeanne M
Fox/LAKE/PPRD/ABBOTT
11/20/2000 04:11 PM

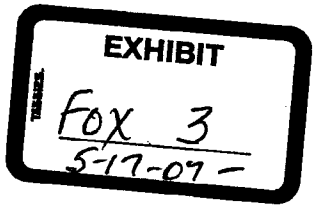
To: John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT, Jerald J Wenker/LAKE/PPD/ABBOTT@ABBOTT, Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT
Arthur J Higgins/LAKE/PPD/ABBOTT@ABBOTT, Carl Craft/LAKE/PPRD/ABBOTT@ABBOTT, George Aynilian/LAKE/PPRD/ABBOTT@ABBOTT, Reid Patterson/LAKE/PPRD/ABBOTT@ABBOTT, Julia Y Hui/LAKE/PPRD/ABBOTT@ABBOTT, William M Bracken/LAKE/PPRD/ABBOTT@ABBOTT, Maria M Paris/LAKE/PPRD/ABBOTT@ABBOTT, Joaquin M Valdes/LAKE/PPRD/ABBOTT@ABBOTT, David D
cc: Morris/LAKE/PPRD/ABBOTT@ABBOTT, Jie X Zhang/LAKE/PPRD/ABBOTT@ABBOTT, Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Robert K Flamm/LAKE/PPRD/ABBOTT@ABBOTT, Linda E Gustavson/LAKE/PPRD/ABBOTT@ABBOTT, Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT, Rod M Mittag/LAKE/PPD/ABBOTT@ABBOTT, Linda J Swanson/LAKE/PPRD/ABBOTT@ABBOTT, Cheryl D Spencer/LAKE/PPRD/ABBOTT@ABBOTT
bcc:
Subject: FDA Telephone Contact Report ABT-773

Attached is a contact report for a teleconference that was held with FDA today concerning ABT-773. We are now officially on clinical hold until further discussion at the End-of-Phase 2 meeting scheduled for November 27, 2000.

Call me if you have questions,

jeanne

FDA Contact Reportdoc.dc



FDA Contact Report

Compound/Product Discussed: ABT-773 Date of Contact: November 20, 2000
Application Type & Number: IND 57,836

	Name & Title	Group
FDA Person(s) Contacted	Dr. Janice Soreth, Acting Division Director	Division of Anti-Infective Drug Products
	Dr. Mercedes Albuerne, Supervisory Medical Officer	
	Dr. Alma Davidson, Medical Officer	
	Dr. Bob Osterberg, Supervisory Pharm/Tox Reviewer	
	Dr. Terry Peters, Pharm/Tox Reviewer	
	Maureen Dillon-Parker, CSO	
Abbott Representatives	Jeanne Fox	Regulatory Affairs
	Greg Bosco	"
	Carl Craft	Venture
	George Aynilian	"
	Reid Patterson	Drug Safety
	Bill Bracken	"
	Julia Hui	"

Subject of Call: FDA requested this teleconference to talk about some "toxicology issues" prior to our End-of-Phase 2 meeting scheduled for next week (November 27, 2000).

Report of Call: The meeting began with introductions, then Maureen said she was filling in for our CSO, Jose Cintron, and asked if we had been told the subject of the call. I told her we understood the purpose to be tox, but had no specifics. Dr. Peters then began by saying that she reviewed our 3 month monkey toxicology study as well as the inspection report and has several concerns about the study. First, there is a concern because the FDA investigator found that there was active drug in some of the control samples. Second, they have knowledge which they cannot share with us regarding similar drugs that has convinced them that the monkey is not a sensitive enough species to look for the two primary toxicities they are worried about with macrolides and ketolides, hepatotoxicity and QT changes. They had advised us of their recommendation that we use the dog after the results of the one month monkey tox study, and now they are looking at a 3 month study in monkeys that they believe is flawed. Reid explained the rational behind not using the dog since our early work in dogs indicated that emesis became so pronounced in dogs that we were unable to reach significant drug exposures, therefore we switched to monkeys. They asked whether we had done QT assessment in this study and we responded no, that our QT evaluation was done by the safety pharmacology group. They responded that they were looking for QT assessment on multiple dosing in toxicology studies, not the kind of information that came out of single dose pharmacology studies. They then stated that to meet the requirement to start phase 3, they need chronic toxicology done in two species and so they want us to do a 30-day dog study with full QT assessment done by telemetry and evaluation for hepatotoxicity. I pointed out that we have provided in our pre-meeting package specific analyses of both our hepatic safety evaluations and our QT monitoring results from the 900 plus patients that we have treated in Phase 1 and 2. Reid stated that since nothing significant was seen in any of the human data it would seem somewhat meaningless to go back and do the dog study. FDA asked to put us on hold.

When they came back after 5 minutes they said they would propose a compromise, and instead of a 30 day study, they would require a two week dog study with special emphasis on hepatotoxicity and QT, with telemetry and with a

recovery period. We agreed that it may be possible to run such a study, although we still have concerns about getting adequate exposures in the dog. I then said that our bigger concern was allowing this tox request to delay our phase 3 studies, and asked if it would be acceptable to run the tox study concurrently since the Phase 3 studies had already started. Based on FDA's reaction it was clear they were unaware that we have begun our studies. Dr. Soreth asked how we could do that prior to our end-of-phase 2 meeting. I pointed out that we had first requested a meeting in July, and it has been scheduled and rescheduled several times. I referenced the letter I sent to her in October when they cancelled the scheduled meeting the last time, which told her we would begin our trials the second week in November. I also referred to the new protocol amendments that were submitted over the last several weeks initiating the studies. She said they expected us to send the protocols to them and wait for comments before proceeding. I explained that we have received comments on at least one of the protocols and parts of the others. She wanted to know if our recent submissions stated we were planning to enroll patients now. I responded that these are our standard study start-up submissions that include information on a minimum of one investigator who can then enroll patients. I explained that we have several patients currently enrolled. Dr. Soreth was not happy with this information, and FDA put us on hold again.

When FDA came back off hold Dr. Soreth told us that they were not expecting us to begin our phase 3 studies prior to the end-of-phase 2 meeting, and that they want us to suspend enrollment at this time. In other words, we are now on clinical hold with these studies. They will discuss this information further prior to the meeting next Monday. I asked whether the 1 hour that has been allotted us next Monday will be enough. Dr. Soreth responded that it will have to be. She indicated they are probably still going to require a dog study. I commented that we do have in writing from Dr. Peters that the three-month study in monkeys should be acceptable to fulfill the requirement. We received this in response to our argument against using dog when they first raised it last year. They did not have the reviewers document in front of them, and Dr. Peters could not recall it, so they said they would go back and look through their records, She also stated that regardless, they would still have issues with the quality of the 3 month study. Reid promised to provide a written response to the issue of active drug in control samples, stated again that there was nothing significant enough to invalidate the study, and questioned whether we could get the exposures they were looking for in dogs. Dr. Peters commented that other sponsors with drugs like these manage to do dog studies. We agreed to provide an estimated timeline for a two-week dog study at Monday's meeting.

We suggested to Dr. Soreth that they also review the QT and hepatic safety assessments that were done in phase 2 since those were done at doses up to 600 mg, so there is more exposure in those phase 2 studies than we will have in phase 3. She said they will look at it.

Action Items: Provide a chronology showing all of the delays in getting the phase 2 meeting to happen as well as the submission of the protocols for review and the response from Dr. Peters acknowledging the 3 month monkey study as acceptable. Prepare a written response regarding the positive study drug in controls from the 3 month tox study.

Deposition Exhibit 4

P's Exhibit IG

Jeanne M Fox/LAKE/PPRD/ABBOTT
11/29/2000 01:48 PM

To: Rod M Mittag/LAKE/PPD/ABBOTT@ABBOTT, Carl Craft/LAKE/PPRD/ABBOTT@ABBOTT, George Ayrsillan/LAKE/PPRD/ABBOTT@ABBOTT
cc: Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT, Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT
bcc:
Subject: Slides for 12/5 meeting

OK, here's my first draft of slides for the Leiden meeting. Please feel free to make comments or redirect me if you think I'm missing something. I guess I think after our meeting on Monday, the only major issues identified which are still open are QT, liver, and resistant pathogens, so that's what I focussed on with some general comments at the end.

jeanne

p.s I apologize for the separate files. I am obviously not as good on my PC as Rod is

Leidenslides1.ppt Leidenslides2.ppt leidenslides3.ppt leidenslides4.ppt leidenslides5.ppt leidenslides6.ppt

EXHIBIT
Fox 4
5-17-07

ABT-773 Regulatory Status

- Original U.S. Oral IND submitted 2/2/99
- Phase 3 pivotal trials initiated 11/00
- End-of-Phase 2 Clinical FDA meeting 11/27/00
- End-of-Phase 2 CMC FDA meeting target 1/01
- Tablet NDA submission target 8/02

ABT-773 Regulatory Issues

- ABT-773 Potential for QT Prolongation
  - QT issue is hot button for FDA
  - Question whether ketolides behave like macrolides
  - FDA requested additional dog tox work to evaluate QT
  - Required to include ECG monitoring in pivotal Phase 3 studies

ABT-773 Regulatory Issues

- ABT-773 Potential for QT Prolongation (continued)
  - telithromycin (Ketek) data residing at FDA
    - Advisory Meeting scheduled for January
- FDA may require a Phase 1 study in patients with underlying cardiac disease
- Some antimicrobials now contain warnings for QT prolongation

ABT-773 Regulatory Issues

- ABT-773 Potential for Liver Toxicity
  - Ketolides similar to macrolides?
  - Request for additional dog tox work
  - telithromycin (Ketek) data residing at FDA
    - Advisory meeting scheduled for January
- Plan to conduct routine liver monitoring in all Phase 3 studies

ABT-773 Regulatory Issues

- Indication to treat resistant pathogens
- FDA skepticism regarding clinical significance of "macrolide-resistant *S. pneumo*"
- FDA will require "body of evidence"
  - excellent eradication of susceptible organisms
  - > 10 resistant organisms eradicated to include good proportion of bacteremic CAP patients

ABT-773 Regulatory Issues

- Miscellaneous
  - Based on NDA timing, potential good candidate for E-submission
  - Timing of IV program may affect ability to document effectiveness vs. resistant pathogens in bacteremic patients
  - Timing of pediatric program and "due diligence" for formulation development critical

Deposition Exhibit 5

P's Exhibit IE

FDA Contact Report

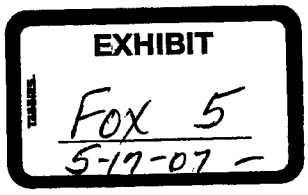
Compound/Product Discussed: ABT-773 - End of Phase 2 Meeting

Application Type & Number: IND 57,836 Date of Contact: November 27, 2000

	Name & Title	Group
FDA Person(s) Contacted	Jose Cintron, Sr. Project Mgr	Anti Infective Division
	Mercedes Albuerne, Medical Team Leader	"
	Nasim Moledina, Medical Officer	"
	Mamodikoe Makhene, Medical Officer	"
	Alma Davidson, Medical Officer	"
	Daphne Lin, Statistics Team Leader	"
	Erica Brittain, M.D., Statistics Reviewer	"
	Terry Peters, Pharm/Tox Reviewer	"
	Robert Osterberg, Pharm/Tox Team Leader	"
	Lilian Gavrilovich, Deputy Director	"
	Charles Bonapace, Biopharm Reviewer	"
	Frank Pelsor, Biopharm Team Leader	"
	Sousan Altnie, Micro Reviewer	"
	Jean Mulinde, Medical Officer	"
	Jim Timper, Chemistry Reviewer	"
	Charles Cooper, Medical Officer	"
	Albert Sheldon, Micro Team Leader	"
	Janice Soreth, Acting Division Director	"
	John Alexander, Medical Officer	"
	Diane Murphy, Office Director	Office of Drug Evaluation - IV
Abbott Representative(s)	Greg Bosco, Sr. Product Mgr	Regulatory Affairs
	Jeanne Fox, Director	Regulatory Affairs
	Jie Zhang, Statistician	Clinical Statistics
	Joaquin Valdes, Physician	Anti Infective Venture
	Carol Meyer, Operations Manager	Anti Infective Venture
	Bob Flamm, Microbiologist	Microbiology
	Linda Gustavson, Pharmacokineticist	Clinical Pharmacokinetics
	David Morris, Statistician	Clinical Statistics
	Maria Paris, Physician	Anti Infective Venture
	George Aynilian, Associate Venture Head	Anti Infective Venture
	Carl Craft, Venture Head	Anti Infective Venture
	John Leonard, Vice President	Research & Development
	Reid Patterson, Vice President	Drug Safety

Subject of Meeting:
The purpose of the meeting was to introduce the oral tablet Phase 3 development plan, discuss potential issues, and address any questions regarding the plan or Phase 2 study results.

Report of Meeting:
The meeting began with introductions from both sides. As Carl began his presentation, Dr. Soreth stated that in case there was some misconception regarding the result of the telecon held on 11/20/00, she wanted to say that the ABT-773 program was at this point not on clinical hold.



Carl began his presentation with a slide showing the proposed indications and treatment durations we were planning to file in the NDA. He showed a series of slides which summarized all the Phase 3 studies we are planning; those starting in 2000 and those slated for 2001. This was the first time FDA saw the proposed dose-selection studies for pneumonia (CAP) and sinusitis (ABS). Dr. Brittain had a few questions regarding the objectives of the studies and the proposed interim analyses, but stated that she would be faxing us all of her comments in more detail. Carl stated that the objectives of the studies were: to pick a dose for the large, well-controlled, comparative, pivotal studies to be conducted in 2001, and to meet the specific pathogen criteria as required for the second supportive trials in the FDA guidance for CAP and ABS. There was lengthy discussion around these study designs. It was stressed to FDA that we still intend to conduct a large, well-controlled, double-blind, comparative trial for each of these indications. FDA advised us there might be a problem using Augmentin 875 mg BID for the sinusitis trial. They would prefer us to use 500 mg TID. Carl committed that we would provide the results from these two trials to FDA for review.

The next slide shown detailed our intention to request a claim for macrolide and penicillin resistant bacteria and atypical bacteria, and the supporting data we proposed to provide to support these claims. Dr. Albuerne stated that we could pool isolates for CAP and ABECB but not for ABS (we proposed pooling from all three). Dr. Soreth stated that there is currently no guidance document available addressing specific requirements for resistant claims but mentioned that there is data from other products (e.g. levofloxacin) that is available in the public domain. As far as our proposal for number of isolates, numbers >10 would be acceptable with good data for susceptible pathogens, but there has been an instance (with linezolid) where <10 was not approvable, but in that case only one or two patients had bacteremia and responded well to therapy. It was stated that a number of bacteremic patients would be required in order to adequately evaluate clinical success against penicillin resistant *Strep pneumoniae*. The comment was made that with oral therapy alone we would probably be hard pressed to find enough patients with bacteremia, that oral/IV therapy gave us a better chance. Dr. Soreth stated that FDA has not seen data supporting "macrolide resistant *Strep pneumoniae*" as a clinical concern. They also said that there is no good body of evidence supporting macrolide resistant *Strep pyogenes* either.

The next topic discussed was the ECG monitoring plan regarding the six Phase 3 studies starting in 2000. We proposed that ECG's would be performed in 5/6 of the studies. In total, we would be gathering ECG data on ~2000 subjects exposed to ABT-773. ECG's will be performed pre-, during, and post-therapy. Additionally, the timing of the ECG and the timing of the dose before the ECG will be documented. FDA requested that we amend all informed consents to mention possible effects on cardiac repolarization caused by ABT-773. Various examples of wording was then discussed and we agreed that we would amend the informed consents for all IND studies. Dr. Soreth asked why we were not doing ECG's in the sixth study. Carl stated that the European pharyngitis study would not include ECG's based on recommendations of our European advisors based on the number of existing visits and the likelihood of subject reluctance to participate in a trial for this disease with so many visits. FDA strongly disagreed with this justification. Dr. Murphy expressed concern that we were blatantly misinforming the subjects in that trial by not including a procedure that would monitor a potentially serious adverse event that was being included in all other studies. This issue was left unresolved. Other comments regarding the collection of a blood sample taken at the on-therapy ECG, etc. were made. All issues were addressed in a subsequent written correspondence by FDA (faxed 12/5/00, Abbott response 12/14/00).

Relating to the topic of possible adverse effects on cardiac repolarization, the results of the previously submitted toxicology studies were discussed. Dr. Peters requested additional data in the dog model. The requested study should be a two-week acute study with telemetry and the study can run concurrent with the Phase 3 clinical trials. At this point Reid offered to provide some background information. He indicated that the emetic activity of ABT-773 in the unanesthetized dog limits exposure in this species, leading to our selection of the cynomolgus monkey as the non-rodent model. While the primate did not indicate a risk for QTc prolongation, exposures of 17 times the human Cmax in anesthetized dogs did lead to some prolongation. Owing to differences in protein binding, the dog receives about 3 times the amount of unbound drug than does the human with identical exposures, perhaps expanding our margin of safety. Various proposals for the study were discussed between Reid and Drs. Peters and Osterberg. We committed to sending draft protocols to Dr. Peters for review.

Carl briefly discussed the Phase 2 ECG data. Dr. Soreth informed us that they have begun to ask for special population studies with drugs that show an effect on ECG's. In this case they would be looking at a study in otherwise healthy subjects with underlying cardiovascular disease. She commented that only looking at the effects

of ABT-773 in comparator trials might not be realistic (i.e., cisapride and terfenadine looked safe in the clinic too). Dr. Murphy commented that it is in both of our best interests to get all the information we can to show how to use the drug safely.

The rest of the meeting was spent answering specific questions regarding the four main Phase 3 trials (CAP, ABS, ABECB & pharyngitis). Most of the comments related to minor protocol changes. All of the issues discussed were subsequently provided to Abbott by fax on 12/5/00. Abbott formally responded to the fax in IND 57,836, Serial No. 066, dated 12/14/00.

Action Items:

- Amend Phase 3 informed consents to incorporate statements relating to: possible effects on cardiac repolarization caused by ABT-773, possible interactions with other drugs, and stronger precautions for women of childbearing potential.
- Provide full narratives from Phase 2 studies of all patients who had an adverse event of syncope or elevated liver enzymes.
- Submit draft toxicology protocol(s) for comment prior to initiating the studies.
- Submit results from CAP and ABS dose-selection trials when available.
- Submit draft protocols for the two well-controlled, comparative, pivotal studies for CAP and ABS (to be conducted in 2001) for comment as soon as available.

Deposition Exhibit 6

P's Exhibit IF

Jeanne M
Fox/LAKE/PPRD/ABBOTT
11/28/2000 09:27 AM

To: Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT, Jerald J Wenker/LAKE/PPD/ABBOTT@ABBOTT, Rosemarie K Waleska/LAKE/PPD/ABBOTT@ABBOTT, Rod M Miltag/LAKE/PPD/ABBOTT@ABBOTT, Arthur J Higgins/LAKE/PPD/ABBOTT@ABBOTT, Linda J Swanson/LAKE/PPRD/ABBOTT@ABBOTT, Mike Rubison/LAKE/PPRD/ABBOTT@ABBOTT, Walid Awni/LAKE/PPRD/ABBOTT@ABBOTT

cc: John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT, Carl Craft/LAKE/PPRD/ABBOTT@ABBOTT, George Aynilian/LAKE/PPRD/ABBOTT@ABBOTT, Reid Patterson/LAKE/PPRD/ABBOTT@ABBOTT, David D Morris/LAKE/PPRD/ABBOTT@ABBOTT, Jie X Zhang/LAKE/PPRD/ABBOTT@ABBOTT, Linda E Gustavson/LAKE/PPRD/ABBOTT@ABBOTT, Joaquin M Valdes/LAKE/PPRD/ABBOTT@ABBOTT, Maria M Paris/LAKE/PPRD/ABBOTT@ABBOTT, Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT

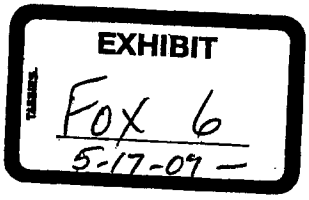
bcc:

Subject: Executive Summary of ABT-773 End-of-Phase 2 Mtg w/ FDA

Yesterday (11/27) the Abbott people on the CC list met with FDA's Anti-Infective Division for the End-of-Phase 2 meeting on ABT-773. Prior to the meeting we had been placed on clinical hold in a teleconference last Monday (11/20). Following are the high points from yesterday's meeting. Detailed minutes of the meeting will be distributed at a later time.

The meeting was generally successful. FDA stated that we are no longer on clinical hold and may proceed with our Phase 3 trials. They have requested additional toxicology work be done to evaluate QT in dogs, but the study can be done concurrently with Phase 3 and they will consider study design proposals from Abbott. FDA accepted the design for the CAP and sinusitis dose-selection studies, although they suggested changes to the statistical analyses for these studies. While FDA acknowledged that our proposal for 15 resistant isolates/pathogen to support a claim for resistant organisms looked reasonable, they will need a good, solid body of evidence. They cautioned us that they have not seen a body of data that supports macrolide resistant Strep pneumo as a clinical concern. They also advised us that we would need to include bacteremic CAP patients with resistant pathogens in order to secure an indication, which would be difficult to do with an oral drug. The FDA reviewers provided a number of recommended protocol changes, most of which are minor to actual study conduct. In addition, we were directed to modify all of our informed consents to inform patients that QT prolongation has been seen with related classes of drugs and therefore may be a risk with ABT-773.

jeanne



Deposition Exhibit 8

P's Exhibit IO

ABT-773 Update February 12, 2001

Introduction

ABT-773 is a ketolide antimicrobial, an evolutionary step from the macrolide antimicrobials such as erythromycin and the new generation macrolides like clarithromycin and azithromycin. It is in phase III development as a replacement to clarithromycin.

The antibiotic market is a large market ($20.5 Billion in 1999) and is expected to expand on a global sales basis ($26.5 Billion in 2005). The majority of the markets sales are in the oral tablet/capsule segment. Market sales increases are being driven by replacement of older/cheaper agents with branded agents. Zithromax has driven market demand for cost/convenience/tolerability, while the quinolones (Levaquin, Tequin, Avelox) are the fastest growing segment, playing into resistance concerns. Resistance is a major driving force for both the quinolones and ketolides development.

Ketolides are a Novel Class of Antimicrobial

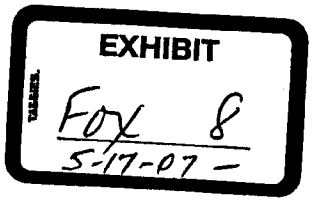
- Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant *S. pneumoniae and S. pyogenes*
- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

ABT-773 is the most active ketolide presently under development. It is 5 to 10 times more active than telithromycin (Aventis ketolide) against *S. pneumoniae* and *S. pyogenes* including resistant strains. It has equal activity to telithromycin and azithromycin against *H. influenzae*. The increased activity can be attributed increased ribosomal binding. Compared to macrolides that bind only to domain V, ABT-773 binds to both domains II and V. The binding is essentially irreversible and provides bactericidal activity against *S. pneumoniae*.

Key issues facing the ABT-773 development program are summarized below

QTc Issues

The potential for QTc prolongation is currently a prominent issue facing drug development across therapeutic areas-worldwide. Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies. There is considerable scientific uncertainty in relating the findings from in vitro assays and animal models to clinical risk of malignant arrhythmias. In an effort to gain more



knowledge these agencies are requiring the pharmaceutical companies to do additional test including

- ICH guidelines require data from animal models and 200 patients
- FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
- FDA has question whether ketolides behave like macrolides
- FDA requested additional dog tox work to evaluate QTc of ABT-773
- ABT-773 studies required including ECG monitoring in pivotal Phase 3 studies.
- FDA may require a Phase I study in patients with underlying cardiac disease, but the design for these studies has not been determined.
- Some antimicrobials now contain warnings for QT prolongation such as moxifloxacin.
- Telithromycin (Ketek) data residing at FDA will be reviewed by FDA Advisory Committee at a meeting scheduled for May 2001 probably related to concerns about efficacy and not related to QTc concerns.

The ketolide ABT-773 will be considered guilty until proven innocent because it is related to erythromycin and clarithromycin which are also suspect and under scrutiny. ABT-773 has the following data related to its potential or lack of potential to affect the QT interval.

- Preclinical data positive for QTc dose response.
- A possible dose effect in Phase I at total daily dose $\geq$800 mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 Cmax 5X)
- No concentration response in Phase I studies ($\leq$300mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)

The Venture plan for dealing with the uncertainties related to developing a drug which has an unknown potential for prolonging the QT intervals is to pro-actively attempt to find out as much about our drug and the science related to QTc by;

- Completed preclinical evaluation of ABT-773
- Initiate FDA recommended dog studies.
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Perform FDA requested study of QTc in patients with pre-existing cardiac disease; perform phase I study as required by CPMP.
- IV ABT-773 Phase I study will monitor QTc carefully
- Consult with Drs. Morganroth and Moss QTc advisors.

Liver Toxicity Issues

The FDA has similar concerns regarding the potential for liver toxicity of new drugs as it has for QTc issues, since both of these problems have resulted in

drugs being removed from the market shortly after approval. The concerns have been directed at the quinolones, but all antimicrobials are under going extensive evaluations. The FDA has a meeting on guidance to industry on how to study the potential for liver toxicity, scheduled for February 11-12, 2001. Jean Fox will attend this meeting and report back on it so that we will be able to update this topic at the February meeting.

In the Japanese bridging study run in Hawaii we saw increases in LFTs in Japanese subjects. This was very disturbing, since increases in LFTs were seen only in the Japanese subjects. In addition the Japanese subjects had AUCs which were 50% higher than the western subjects. LFTs in over 1000 western subjects did not show any problems. Since, the Japanese subjects with elevated LFTs did not show a dose response, it was felt that the changes in LFTs might be related to the high caloric diet on the unit. To answer this question Phase I food interaction and a repeat of the bridging study was preformed in Japan. The results of this study showed no evidence of any problem with LFTs in the Japanese or Caucasians. Based on the encouraging results we will continue moving forward with the Japan Program.

Phase III Tablet Program

The Phase III tablet program is underway after several delays related to manufacturing of the 150 mg tablet to replace the 300 mg tablets and the late date (11/27/00) of the FDA End of Phase II meeting. The present plan is to complete the Phase III 150 mg once daily indications in the US and Europe this year. These studies include two pharyngitis studies compared to penicillin 500 mg TID, one ABECB study in the US compared to Azithromycin, and one European ABECB study compared to Levofloxacin. The CAP and sinusitis dose selections studies are running globally, but no European sites are enrolling yet due to the changes in the protocol following the FDA End of Phase II meeting. We are increasing sites and planning to go to the Southern Hemisphere if needed to complete the studies before the start of the fall respiratory season. These changes have added additional costs that will add approximately $5.0 MM to the budget.

The results of the CAP and Sinusitis studies have the potential of generating divergent development paths based on differences in AI and PPD regulatory and commercial considerations. PPD would prefer to have 150 mg once daily for all indications and AI would prefer 150 mg once daily for pharyngitis and ABECB and 150 mg BID for CAP and sinusitis. Once we complete the study we will need to meet to iron out the possible options.

ABT-773 IV Formulation Program

The IV formulation program is presently unfunded. The IV program is important to overall program because of the following;

- Hospital formulary acceptance
- XX% share gain in Tab sales due to step-down therapy
- Positions 773 for serious infections
- Support for *S. pneumoniae* resistance claim
  - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provide additional information on QTc effects

The ABT-773 IV program received partial funding last year both from PPD and HPD, but has not been funded for 2001. The following outlines the IV program fund and funding needed.

- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 ($1.4MM)
  - Formulation development (lactate salt, lyophilized powder)
  - Animal pain models
  - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 ($0.8MM)
  - Two week Tox study (rat)
  - Clinical supplies for Phase I
  - Stability program
- 2001 funding
  - HPD first pass funding cut for 773 IV ($7MM)
  - Milestone funding to Phase I Go/No Go ($1MM)
- Total program development costs 2000 - 2003 ($22.5MM)

The clinical program with 2001 funding decision in February will included;

- Single Dose-rising Phase I study — Apr/01
- Multiple Dose Phase I with selected dose — June/01
- File US IND — Oct/01
- Initiate Phase III — Dec/01
  - 2 step-down CAP studies (US/Europe)
  - 2-3 days dosing
  - Two seasons to complete
- Filing — Aug/03

The Venture would recommend funding the Phase I study to determine safety and tolerability profile as a GO/No Go decision. Assuming a GO decision we would need $7 MM 2001 to start Phase III program.

Pediatric Program

The pediatric suspension program is on hold. ABT-773 is 5 to 7 times more bitter than clarithromycin. This will make the development of an acceptable formulation very difficult. The first prototype tested had a taste that was better than clarithromycin but not as good azithromycin. The pharmacokinetics showed AUCs that were only 70% of the tablet formulation. Even with the difficulties of making an acceptable formulation the pediatric formulation would have benefits including increasing the perception of safety, better pricing and acceptance in European markets, and FDA requires studies in pediatrics. The Venture would recommend continuing the hold until we resolve other issues and then re-evaluate possible ways of overcoming the taste problem.

Japan Development Program

The Japan development program is planned in coordination with Taisho and Dainabot. Taisho funds 10.69% of global development costs and 50% of local Japan costs. The Venture is attempting to use a bridging strategy is the primary plan for development in Japan. The Phase I studies in Japan which were initiated in response to the LFT problems in the first bridging study, have been completed. There were not increases in the LFTs of the Japanese or Caucasians in the study. We will be meeting with Taisho and Dainabot to formulate a plan to present to Kiko in the 2nd or 3rd Quarter.

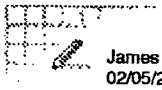
Deposition Exhibit 10

P's Exhibit IQ

Jeanne M Fox/LAKE/PPRD/ABBOTT
02/14/2001 01:04 PM

To James Steck/LAKE/PPRD/ABBOTT@ABBOTT
cc Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject Re: Studies to Meet Pediatric Rule Requirements

I share your concern and have an even bigger one In those cases where we are planning to develop an NCE, and we have a target NDA date, I have had difficulty convincing people they have to take the pediatric rule requirements seriously. The answer I keep getting on ABT-773 is "but that project isn't funded". I don't think FDA will buy that answer.
James Steck



James Steck
02/05/2001 05:20 PM

To: Jeanne M Fox/LAKE/PPRD/ABBOTT@ABBOTT, Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Studies to Meet Pediatric Rule Requirements

Jeanne and Mick

This is just a heads up to let you know that there may be some issues arising in the future about concerns for being able to do studies requested by FDA to meet pediatric rule requirements because these studies "are not funded". Steve and I are runnning into discussions on this for Depakote ER in migraine where FDA has asked us to do an efficacy study in migraine per the the pediatric rule Of course we will attempt to negotiate with FDA to do the least onerous studies that will still satisfy the pediatric rule requirments, but folks will need to advised at some point (preferably early on) that meeting this rule is a regulatory obligation and a cost of doing business. I'd appreciate hearing any thoughts you have on this subject.

Jim